BICYCLIC PEPTIDE LIGANDS SPECIFIC FOR NECTIN-4

FIELD OF THE INVENTION

[0001] The present invention relates to polypeptides which are covalently bound to molecular scaffolds such that two or more peptide loops are subtended between attachment points to the scaffold. In particular, the invention describes peptides which are high affinity binders of Nectin-4. The invention also includes drug conjugates comprising said peptides, conjugated to one or more effector and/or functional groups, to pharmaceutical compositions comprising said peptide ligands and drug conjugates and to the use of said peptide ligands and drug conjugates in preventing, suppressing or treating a disease or disorder mediated by Nectin-4.

BACKGROUND OF THE INVENTION

[0002] Cyclic peptides are able to bind with high affinity and target specificity to protein targets and hence are an attractive molecule class for the development of therapeutics. In fact, several cyclic peptides are already successfully used in the clinic, as for example the antibacterial peptide vancomycin, the immunosuppressant drug cyclosporine or the anti-cancer drug octreotide (Driggers et al. (2008), Nat Rev Drug Discov 7 (7), 608-24). Good binding properties result from a relatively large interaction surface formed between the peptide and the target as well as the reduced conformational flexibility of the cyclic structures. Typically, macrocycles bind to surfaces of several hundred square angstrom, as for example the cyclic peptide CXCR4 antagonist CVX_{15} (400 $Å^2$; Wu et al. (2007), Science 330, 1066-71), a cyclic peptide with the Arg-Gly-Asp motif binding to integrin aVb3 (355 $Å^2$) (Xiong et al. (2002), Science 296 (5565), 151-5) or the cyclic peptide inhibitor upain-1 binding to urokinase-type plasminogen activator (603 $Å^2$; Zhao et al. (2007), J Struct Biol 160 (1), 1-10).

[0003] Due to their cyclic configuration, peptide macrocycles are less flexible than linear peptides, leading to a smaller loss of entropy upon binding to targets and resulting in a higher binding affinity. The reduced flexibility also leads to locking target-specific conformations, increasing binding specificity compared to linear peptides. This effect has been exemplified by a potent and selective inhibitor of matrix metalloproteinase 8 (MMP-8), which lost its selectivity over other MMPs when its ring was opened (Cherney et al. (1998), J Med Chem 41 (11), 1749-51). The favorable binding properties achieved through macrocyclization are even more pronounced in multicyclic peptides having more than one peptide ring as for example in vancomycin, nisin and actinomycin.

[0004] Different research teams have previously tethered polypeptides with cysteine residues to a synthetic molecular structure (Kemp and McNamara (1985), J. Org. Chem; Timmerman et al. (2005), ChemBioChem). Meloen and co-workers had used tris(bromomethyl)benzene and related molecules for rapid and quantitative cyclisation of multiple peptide loops onto synthetic scaffolds for structural mimicry of protein surfaces (Timmerman et al. (2005), ChemBioChem). Methods for the generation of candidate drug compounds wherein said compounds are generated by linking cysteine containing polypeptides to a molecular scaffold as for example TATA (1,1',1"-(1,3,5-triazinane-1,3,5-triyl) triprop-2-en-1-one, Heinis et al. Angew Chem, Int Ed. 2014; 53:1602-1606).

[0005] Phage display-based combinatorial approaches have been developed to generate and screen large libraries of bicyclic peptides to targets of interest (Heinis et al. (2009), Nat Chem Biol 5 (7), 502-7 and WO 2009/098450). Briefly, combinatorial libraries of linear peptides containing three cysteine residues and two regions of six random amino acids ($(Cys-(Xaa)_6-Cys-(Xaa)_6-Cys)$ were displayed on phage and cyclised by covalently linking the cysteine side chains to a small molecule scaffold.

SUMMARY OF THE INVENTION

[0006] According to a first aspect of the invention, there is provided a peptide ligand specific for Nectin-4 comprising a polypeptide comprising at least three cysteine residues, separated by at least two loop sequences, and a molecular scaffold which forms covalent bonds with the cysteine residues of the polypeptide such that at least two polypeptide loops are formed on the molecular scaffold.

[0007] According to a further aspect of the invention, there is provided a drug conjugate comprising a peptide ligand as defined herein conjugated to one or more effector and/or functional groups.

[0008] According to a further aspect of the invention, there is provided a pharmaceutical composition comprising a peptide ligand or a drug conjugate as defined herein in combination with one or more pharmaceutically acceptable excipients.

[0009] According to a further aspect of the invention, there is provided a peptide ligand or drug conjugate as defined herein for use in preventing, suppressing or treating a disease or disorder mediated by Nectin-4.

BRIEF DESCRIPTION OF THE FIGURES

[0010] Where present in the figures, error bars represent standard error of the mean (SEM).

[0011] FIGS. **1** to **7**: Tumor volume traces after administering BCY7683, BCY7825, BCY7826, BCY8245, BCY8253, BCY8254 and BCY8255, respectively, to female BALB/c nude mice bearing NCI-H292 xenograft.

[0012] FIGS. **8** to **10**: Tumor volume traces after administering BCY8245, BCY8253 and BCY8255, respectively, to female Balb/c nude mice bearing NCI-H292 xenograft.

[0013] FIGS. **11** to **15**: Tumor volume traces after administering BCY7825, BCY8245, BCY8253, BCY8254 and BCY8255, respectively, to female CB17-SCID mice bearing HT-1376 xenograft.

[0014] FIGS. **16** to **18**: Tumor volume traces after administering BCY8245, BCY8253 and BCY8255, respectively, to female CB17-SCID mice bearing HT-1376 xenograft.

[0015] FIGS. **19** to **21**: Tumor volume traces after administering BCY8245, BCY8253 and BCY8255, respectively, to female Balb/c nude mice bearing Panc2.13 xenograft.

[0016] FIGS. **22** to **24**: Tumor volume traces after administering BCY8245, BCY8253 and BCY8255, respectively, to female Balb/c nude mice bearing MDA-MB-468 xenograft.

[0017] FIGS. **25** to **28**: Tumor volume traces after administering BCY8549, BCY8550, BCY8783 and BCY8784, respectively (with BCY8245 as control), to female BALB/c nude mice bearing NCI-H292 xenograft.